Pharmacology
Team 437

MED437
KING SAUD UNIVERSITY

Endocrine final summary file

Color index:
Important
Note
Extra

Editing File

Drugs of Endocrine Block

Osteoporosis		
Drug	**Key Point**	**C.I**
Bisphosphonate	**MOA**: 1-bound to hydroxyapatite, decreasing its solubility and making it more resistant to osteoclastic activity. 2-prevent bone resorption by blocking steps in cholesterol synthetic pathway within osteoclast that act as signalling molecules responsible for hydrolytic and phagocytic activity which leads to osteoclast apoptosis. **USE**: Osteoporosis 2ndry to menopause and steroids/pagets disease/malignancy associated hypercalcemia **ADRS**: -GIT irritation; nausea, vomiting, gastritis , ulceration,esophagitis (give large amount of water to avoid risk of the tablet getting stuck in the esophagus) Gastroesophageal reflux ulcerations to avoid:give on empty stomach while sitting in upright fo r30min -Flu like manifestations -Osteo-necrosis of the jaw (mandible > jaw) esp. After long use through IV infusion after dental procedures. -Atrial fibrillation	If a dental implant or extraction is already planned, delay bisphosphonate therapy for a few months until healing of the jaw is complete -Decreased renal function -Peptic ulcer / esophageal reflux
RANKL inhibitors **Denosumab**	**MOA**: human monoclonal antibody that Mimics osteoprotegerin (OPG) by Binding to RANKL, expressed by osteoblasts→ Block RANKL from interacting with RANK expressed on pre osteoclasts→ decrease Osteoclastogenesis(no mature osteoclasts). Also binds with mature osteoclast → apoptosis **ADRS**: Infections:urinary & respiratory, Pancreatitis, Eczema & skin rash	In patients with hypocalcemia

Drugs of Endocrine Block

Osteoporosis

Drug	Key Point	C.I
Strontium	**Has both anabolic & anti- resorptive effects** resulting in a rebalance of bone turnover in favor of bone formation. Effects on **osteoblasts:** -it acts as agonist on Ca Sensing Receptor [CaSR] → enhances differentiation of preosteoblast to osteoblast.(increase bone formation) - stimulates the expression of OPG → increase RANKL binding → decreases osteoclastogenesis (decrease bone resorption) Effects on **osteoclasts:** it acts as agonist on Ca Sensing Receptor [CaSR] → suppress differentiation of preosteoclast to osteoclast therefore increasing its apoptosis and decreasing bone resorption. **USES:**Osteoporosis 2ndry to menopause and steroids, malignancy associated hypercalcaemia **ADRS:** GIT irritation, headache, eczema(reversible) Interactions: Food specially containing milk+ its products • Antacids & Oral tetracycline & quinolones chelate it (Precautions: 2hrs spacing)	In severe renal disease. In hypersensitivity to it In increased risk of venous thromboembolism In phenylketonuria
Estrogen	**MOA; increase osteoclast apoptosis and inhibit osteoblast apoptosis,** decrease the number and depth or resorption cavities, increase the release of growth factors from osteoblasts, decrease release of inflammatory cytokines causing resorption. **ADRs**: risk of breast cancer,Vaginal bleeding,Venous thromboembolism **USE:** -In hysterectomy: use Estrogen ONLY -if uterus is present use estrogen and progestins As hormonal replacement therapy in Menopausal symptoms Androgens for elderly men ONLY	
SERM Raloxifene	1st selective estrogen Receptor modulator (SERM) Antiestrogens that exhibits partial agonistic action; acting as an agonist in bone & an antagonist in some female sex organs. Used for menopausal symptoms. Advantages: -No need for progestin in women with uterus. -Good for women with risk of uterine and breast cancer. -Lower risk of thromboembolism compared to estrogen disadvantage; May increase hot flushes. No effect on HDL.	

Drugs of Endocrine Block

drugs used in calcium & vitamin D disorders

Drug	Key Point	C.I
Parathyroid Hormone	**Action:** increase plasma Ca2+ levels **By :1-**enhances intestinal calcium absorption in the presence of vitD . **2-**stimulates bone resorption by stimulating osteoclasts to increase the outward flux of calcium. **3-**stimulates the active reabsorption from kidney + increases formation of calcitriol. **Intermittent:** Osteoblast ↑ number/function,↑ Bone formation, ↑ Bone mass/strength **Continuous:** ↑Osteoclast, ↑ Bone resorption, ↑Serum Ca2+ (hyperparathyroidism) **Uses:** Treatment of severe osteoporosis , Resistant cases failed to respond to other medications , it's given SC	
Teriparatide	**MOA:** Synthetic polypeptide form of PTH (PTH analogue).given SC , Once-daily, called "anabolic" **Therapeutic effects:** stimulation of osteoblastic activity over osteoclastic activity. (new bone formation) continuous administration causes bone resorption. **Uses:** postmenopausal osteoporosis, people who have a risk of getting fracture, severe osteoporosis and patients not responding to other drugs. **ADRs:** Carcinogenic effect (osteosarcoma),orthostatic hypotension ,kidney stones,leg cramps	-osteosarcoma -Paget's disease -radiation treatment -in children
Vitamin D	A steroid hormone that is intimately involved in the regulation of plasma calcium levels. **Metabolism:** Vitamin D3 is metabolically inactive until it is hydroxylated in the liver then the kidney by alpha hydroxylase **Sources:** Cholecalciferol (Vitamin D3) in skin , Ergocalciferol (Vitamin D2) in plants, Calcitriol 1,25-dihydroxyvitamin D is the active form **MOA:** ↑ bone resorption, ↑Ca2+ absorption from intestine , ↑ renal Ca2+ and PO4 reabsorption, decreases the production of PTH **(increased plasma calcium concentrations)** **Uses:** Rickets & Osteomalacia, Osteoporosis, Cancer prevention, Psoriasis	
Calcitonin	Calcitonin is synthesized and secreted by the parafollicular cells (C cells) of the thyroid gland.) **MOA:** decrease in plasma Ca2+, By: 1-Inhibit osteoclast activity→ inhibiting bone resorption. 2-Decreasing reabsorption of Ca2+ & PO4 by the kidney, thus ↑ their excretion. **Uses:**hypercalcemia ,Osteoporosis , Paget's disease. **ADRs:** Local inflammation at site of injection , Flushing of face & hands , Nasal irritation	

Drugs of Endocrine Block

Use of Insulin in the treatment of diabetes mellitus

Drug	Key Point	C.I
Ultra-short acting insulins		
-Lispro -Aspart -Glulisine	-**very fast onset** of action and short duration -**Clear solutions at neutral pH** -monomeric analogue -Fast onset of action (5-15 min) -Short duration of action (3-5 h),regardless of the dose: • Decreased risk of hyperinsulinemia. • Decreased risk of postprandial hypoglycemia -Usual administration:2 – 3 times/day **USE**:-Preferred for **external insulin pump** -used to control postprandial hyperglycemia (s.c.) -emergency diabetic ketoacidosis **(i.v)**	
Short-acting insulins (Regular)		
-Humulin R -Novolin R	-**fast onset** of action and short duration. -Clear solutions at neutral pH -Forms hexamers. -Onset of action 30-45 min,Duration 6-8 h. -Usual administration:2 – 3 times/day **USE**:-Can be used in pregnancy,used to control postprandial hyperglycemia (s.c.) -emergency diabetic ketoacidosis (i.v)	
Intermediate acting insulins		
-Isophane (NPH) insulin. -Lente	-**Slow onset**, intermediate duration of action -Turbid suspension at neutral pH. -Given S.C. only not i.v. -Can not be used in ketoacidosis or emergency (NO IV) -Onset of action 1-2 h,Duration of action 13-18 h. - Combined with lispro, aspart or regular insulins.	
Long acting insulins		
-glargine (lantus) -detemir (Levemir)	**-Slow onset and long duration** of action.Clear solution BUT forms precipitate (hexamer) at injection site,should not be mixed with other insulins in the same syringe. (PH sensitive) -Slow onset of action 2 h,Prolonged duration of action (24 h),Given s.c., not intravenously,produce broad plasma concentration plateau, Mimics basal insulin release(low continuous insulin level),peakless profile,safer than NPH & Lente insulins (reduced risk of nocturnal hypoglycemia). **USE**:Used in type 1 and type 2 diabetes.	

Complications of Insulin Therapy

Hypoglycemia,Hypersensitivity reactions,Lipodystrophy (a buildup of fatty tissue) at the injection sites,Weight gain (due to anabolic effects of insulin),Insulin resistance ,Hypokalemia

Management of diabetic ketoacidosis and hypoglycemia.

Diabetic ketoacidosis

-Elevated above **200**
Lines of treatment of diabetic ketoacidosis Adequate correction of :
– Dehydration (Fluid therapy)
– Hyperglycemia (Insulin)
– Electrolyte deficits (Potassium therapy)
– Ketoacidosis (Bicarbonate therapy)

Fluid therapy (Rehydration):
-Restore blood volume and perfusion of tissues.
– Infusion of isotonic saline (0.9% sodium chloride)

Insulin therapy (Short acting insulin):
-Regular insulin, should be administered by means of continuous intravenous infusion in small doses through an infusion pump (0.1 U/kg/h)
-Subcutaneous absorption of insulin is reduced in DKA because of dehydration; therefore, using intravenous routes is preferable.
-Insulin stops lipolysis and promotes degradation of ketone bodies.

Potassium therapy:
-potassium is added to infusion fluid to correct the serum potassium concentration.

Bicarbonate therapy:
-bicarbonate therapy should be used only if the arterial pH < 7.0 after 1 hour of hydration, (sodium bicarbonate should be administered every 2 hours until the pH is at least 7.0).

Hypoglycemia

-Blood sugar of less than 70 mg/dl is considered hypoglycemia.
-Is a life threatening disorder that occurs when blood glucose level becomes < 50 mg/dl l
-One of the common side effects of insulin in treating type I diabetes

Treatment of Hypoglycemia:
Conscious patient:
– Sugar containing beverage or food (30 g orally).
Unconscious patient:
– Glucagon (1 mg S.C. or I.M.)
– 20-50 ml of 50% glucose solution I.V. infusion (risk of possible phlebitis).

Drugs of Endocrine Block

Steroids		
Drug	**Key Point**	**C.I**
Corticosteroid Agonists		
Glucocorticoids		
Cortisol (Hydrocortisone)	- The major natural glucocorticoid **Disadvantages Of cortisol:** - Short duration of action - Diffuses poorly across normal skin & mucous membranes - This is an important cause of hypertension in patients with cortisol secreting adrenal tumor or a pituitary ACTH secreting tumor (Cushing's syndrome).	-
Synthetic Glucocorticoids: - Prednisone - Dexamethasone - Beclomethasone - Budesonide	- Longer half life & duration of action - Reduce salt retaining effect - Better penetration of lipid barriers for topical activity - **Beclomethasone** & **budesonide** have been developed for use in asthma because they rapidly penetrate airway mucosa but have very short half lives in the blood so their systemic effects and toxicity are reduced.	-
Mineralocorticoids		
Aldosterone	- The major natural mineralocorticoid in human. - It is very important in the regulation of blood volume & blood pressure. Its secretion is regulated by ACTH & by the renin-angiotensin system. (promotes Na reabsorption, K excretion, in the DCT) Uses: - **Fludrocortisone** (long duration of action) is favored for replacement therapy after **adrenalectomy** & in other conditions in which mineralocorticoid therapy is needed.	

Steroids

Drug	Key Point	C. I
Corticosteroid Antagonists		
Receptor Antagonists		
Spironolactone	- Antagonists of aldosterone at its receptor **Uses:** - Treatment of primary aldosteronism	-
Eplerenone		-
Mifepristone	- A competitive inhibitor of glucocorticoid receptor, as well as a progesterone receptor **Uses:** - Cushing's syndrome	-
Synthesis inhibitors		
Ketoconazole **Aminoglutethimide** **Metyrapone**	**Ketoconazole:** Inhibit the **cytochrome p450** enzymes necessary for the synthesis of all steroids. **Aminogluthemide:** it **blocks** the conversion of **cholesterol to pregnelone,** it inhibits the synthesis of all **hormonally active steroids.** **Uses of ketoconazole:** - Adrenal carcinoma - Hirsutism - Breast cancer - Prostate cancer Adrenal cancer, when surgical therapy is impractical or unsuccessful because of metastasis. **Uses of Aminoglutethimide:** Adrenocortical cancer (steroid producing tumor) in conjunction with other drugs.	-

Adverse Effects of Corticoids

- Cushing syndrome more than >100mg hydrocortisone for 2 weeks.
- Osteoporosis and aseptic necrosis of the hip.
- Wound healing
- Peptic ulcer
- Psychosis\depression
- Subcapsular cataract
- Growth suppression
- Hypertension
- Adrenal suppression

How to avoid:
Local application - alternate day therapy - tapering the dose after achieving the therapeutic response - give additional stress dose during serious ilness\surgery

Drugs of Endocrine Block

Oral hypoglycemic drugs

Drug	Key Point	C.I
Insulin secretagogues **M.O.A:** Stimulate insulin release from **functioning B cells by blocking of ATP-sensitive K channels** which causes depolarization and opening of voltage- dependent calcium channels, which causes an increase in intracellular calcium in the beta cells, which stimulates insulin release.		
Sulfonylureas (Second generation)		
Short acting: Gliclazide Glipizide **Long acting:** Glyburide Glimepiride	**-P.K:** Orally,Metabolized in liver, Excreted in **urine** & **cross placenta** lead to fetal hypoglycemia at birth. -More potent than first generation,have longer duration of action. **-Uses:** Treatment of Type II diabetes monotherapy or in combination with other antidiabetic drugs. **-ADRs:Hyperinsulinemia**,**Hypoglycemia(**More common in **glyburide & glimepiride** also specially in **old age, hepatic or renal diseases)** & **Weight gain.**	-Pregnancy. With pregnancy we use insulin
Meglitinides		
Repaglinide	**-P.K:** Orally, **Very fast onset of action, Short duration of action,excreted in bile**(When the patient has renal disease we use meglitinides instead of sulfonylurea). **-Uses:** same as Sulfonylureas, also as alternative to sulfonylureas in **patients allergic to sulfonylureas.** **-ADRs:** same as Sulfonylureas **BUT** less incidence than sulfonylureas.(hypoglycemia , weight gain)	-Pregnancy.
Incretins		
Incretins mimetics: Glucagon-like peptide-1 agonists (GLP-1).		
Liraglutide	**-M.O.A:** 1-Binds to GLP-1 receptors & stimulates insulin secretion from β cells. 2-It reduces glucagon secretion by inhibiting alpha cells of the pancreas. 3-It decreases appetite and inhibits body weight gain. **-P.K:** given **s.c** & given as single- dose pre-filled disposable pens. **-Uses:** together with diet & exercise to treat **type 2 DM** and in patients who are **not** controlled with other oral antidiabetics & as a treatment for adults who are obese or overweight with at least one weight- related condition (e.g. hypertension, type 2 DM).	-Pregnancy. -T1DM

Drugs of Endocrine Block

Drug	Key Point	C.I
Incretins mimetics: Glucagon-like peptide-1 agonists (GLP-1). (Cont'd)		
Liraglutide	**-ADRs:** GIT disturbances (nausea,vomiting , diarrhea) Hypoglycemia(combined with sulphonylureas or insulin) & Pancreatitis.	-Pregnancy.
Dipeptidyl peptidase-4 inhibitors (DPP- 4 inhibitors) **-M.O.A: 1-Inhibit DPP-4 enzyme** and leads to an **increase in incretin hormones level.** 2-Increase in insulin secretion & decrease in glucagon secretion.		
Sitagliptin (given orally) **Vildagliptin**	**-Uses:** Treatment for type II DM as an adjunct to diet & exercise as a monotherapy or in combination with other antidiabetic drugs. **-ADRs:** GIT disturbances(nausea, diarrhea, abdominal pain) ,Nasopharyngitis and headache.	-Pregnancy.
Insulin sensitizers **-M.O.A:** Increases the sensitivity of peripheral target organs to insulin.		
Biguanides: metformin	**-M.O.A:** 1-Reduces insulin resistance by Increasing **sensitivity** of **liver**(mainly), muscle & adipose tissues to insulin & **increase peripheral glucose utilization.** 2-Inhibits hepatic glucose production. 3-Impairs glucose absorption from GIT. 4-Improve lipid profile (-) LDL (-)VLDL , (+)HDL. **-P.K:** orally, not bound to serum protein, not metabolized & Excreted unchanged in urine. **-Uses:** In patients with type 2 diabetes who are obese & as monotherapy or in combination. **-Advantages:** has prominent lipid-lowering activity, **No hypoglycemia** & No weight gain. **-ADRs:** GIT disturbances(nausea, vomiting , diarrhea) **Lactic acidosis.** Especially in (renal insufficiency, liver disease,Alcohol abuse, heart failure, pulmonary insufficiency, shock)	- Interference with vitamin B12 absorption (long term use). -Renal & Liver disease. -Alcoholism. -Cardiopulmonary dysfunction. -Pregnancy.

Drugs of Endocrine Block

Drug	Key Point	C.I
Insulin sensitizers (cont'd) **-M.O.A:** Increases the sensitivity of peripheral target organs to insulin.		
Thiazolidinediones		
Pioglitazone	**-M.O.A:** 1-Activate peroxisome proliferator-activated receptor -g (PPAR-g). 2-Increase glucose uptake and utilization in muscle and adipose tissue. **-P.K:** Orally, Slow onset of activity, Metabolized in liver & Excreted in bile and urine. **-Uses:** Type II diabetes either alone or combined with sulfonylurea, biguanides or insulin. **-No risk of hypoglycemia when used alone.** **-ADRs: Hepatotoxicity**, Fluid retention ,**Congestive heart failure, Mild weight gain** & Failure of estrogen-containing oral contraceptives.	-Pregnancy.
a -Glucosidase inhibitors		
Acarbose	**-M.O.A:** 1-**Reversible** inhibitors of **intestinal a-glucosidases** in intestinal brush border cells that are responsible for carbohydrate digestion. 2-**decrease carbohydrate** digestion and glucose absorption in **small intestine** (lower postprandial glucose level). **-P.K:** orally, not absorbed, Excreted in feces & No hypoglycemia if used alone. **-Uses:** effective alone in the earliest stages of impaired glucose tolerance , not recommended alone & are most useful in combination with other oral hypoglycemic drugs or with insulin. **-ADRs:** GIT side effects: **Flatulence**, bloating,diarrhea, abdominal pain.	-Irritable bowel syndrome. -Inflammatory bowel disorders. -Intestinal obstruction. -Pregnancy.
Sodium-glucose transporter 2 (SGLT2) inhibitors		
Canagliflozin	**-M.O.A:** Inhibits SGLT2 in the kidneys. This allows excess glucose to be excreted in the urine. This will reduce blood sugar levels. **-Uses:** with diet and exercise to control high blood sugar in patients with type 2 diabetes. **-ADRs:** Urinary tract infections, Increased urination, dry mouth & Yeast infections.	-Pregnancy.

Team Leaders:

Majed Aljohani Layan AlMana

Thank you to those who worked on this file:

Dimah AlOraifi
Ahad AlGrain
Nouf AlOtaibi
Fatma AlBassam
Ghaida AlSanad

References:

✓ Doctors' slides and notes

@Pharma4370 Pharm437@gmail.com